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The effect of sleep on male reproductive system
A protocol for systematic review and meta analysis

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Abstract
Background: the purpose of this study was to evaluate the effects of sleep deprivation on semen analyses, hormone levels and testicular histopathology in men.

Methods: this review will be included in a qualified case-control study. The search strategy will be implemented in PubMed, Embase, Web of science, Cochrane library, China National knowledge Infrastructure database, Wanfang Database, and the Cochrane library. We will solicit both English and Chinese case-control studies published from its beginning to July 31, 2020. The 2 examiners will independently screen, select research, extract data and evaluate quality. We use Revman5.3 software to generate funnel map, heterogeneity assessment, data analysis, subgroup analysis and sensitivity analysis.

Results: in the current meta-analysis, we will provide some more practical and targeted results for the study of the effects of sleep on the male reproductive system, and sum up the main limitations of previous studies.

Conclusion: this study will provide new evidence for the effect of sleep on male reproductive system.

Abbreviations: MRS = male reproductive system, SA = semen analyses.

Keywords: reproductive system, semen analyses, sleep, systematic review

1. Introduction

Male infertility is considered to be a public-health-epidemic.[1–2] The World Health Organization (WHO)estimates that 8% to 12% of couples worldwide face fertility problems, while male factors cause 50% of the problems.[3] There are many factors causing male infertility, such as environmental pollution, mental stress, smoking, alcoholism, bad lifestyle and so on.[4–7] in recent years, studies have shown that bad living habits can lead to a decline in semen analyses (SA).[8] Therefore, people pay more and more attention to sleep. Sleep is of great significance to human health, which can affect people's nervous, endocrine, immune and cardiovascular system functions. Nevertheless, sleep management is still challenging and has not been fully understood. Therefore, we will conduct a systematic review and meta-analysis

to determine the effects of sleep on SA and hormone levels, and to provide further evidence for health service providers and patients. The purpose of this study is to conduct a systematic review and meta-analysis to determine the effects of sleep on the male reproductive system (MRS).

2. Method

This protocol has been registered on the Open Science Framework (OSF) platform (Registration Number: DOI 10.17605/OSF.IO/3W5AU). We will strictly implement the network meta-analysis of systematic evaluation and meta-analysis reports in compliance with the requirements of the preferred reports. Ethical approval is not necessary for the study.

2.1. Inclusion criteria for study selection
2.1.1. Study types. Case-control studies related to the effects of sleep on the MRS will be included in our evaluation. These studies provided available genotypic frequencies in the case of the group and the control group to estimate the ratio of and its 95% network connection confidence interval. The language, publication date or status of the study will not be subject to any restrictions.

2.1.2. Participant types. Male participants affected by sleep will be included in the meta-analysis. The control subjects were defined as healthy subjects who slept normally. There is no restriction on age or country.

2.1.3. Outcome. SA, containing sperm motility parameters and sperm count, hormone levels, including testosterone levels, corticosterone levels, progesterone levels, testicular pathological changes.

Table 1

Search strategy used in PubMed database.

No	Search items
1	MeSH descriptor: [Sleep Disorders, Circadian Rhythm] explode all trees
2	MeSH descriptor: [Sleep Deprivation] explode all trees
3	MeSH descriptor: [Dyssomnias] explode all trees
4	MeSH descriptor: [Sleep] explode all trees
5	#1 or #2 or #3 or #4
5	MeSH descriptor: [Genitalia, Male] explode all trees
6	MeSH descriptor: [Testis] explode all trees
7	MeSH descriptor: [Seminiferous Epithelium] explode all trees
8	MeSH descriptor: [Spermatozoon] explode all trees
9	MeSH descriptor: [Semen Analysis] explode all trees
10	MeSH descriptor: [Sperm Count] explode all trees
11	MeSH descriptor: [Sperm Motility] explode all trees
12	MeSH descriptor: [Gonadal Hormones] explode all trees
13	MeSH descriptor: [Testicular Hormones] explode all trees
14	MeSH descriptor: [Gonadal Steroid Hormones] explode all trees
15	MeSH descriptor: [Gonadal Hormones] explode all trees
16	#6or #7or #8 or #9 or #10 or #11 or #12 #13 or #14 or #15
17	#5and #16

MeSH = medical subject headings.

2.1.4. Exclusion criteria.
Repetitive reports, conference summaries, case reports, review papers, or animal studies, and so on.

2.1.5. Search strategy.
We will search all the qualified literatures in the China knowledge Network database, database of PubMed, Embase and Web of science. Search time range from the beginning to July 31, 2020 published all Chinese and English literature. In addition, considering unpublished or ongoing trials, or trials that have been completed but ready to be published, we will conduct targeted searches of grey literature on the clinical trial website and the China Clinical Trials Registry. At the same time, the reference list of previous clinical studies and reviews is used as a supplementary source. Take the retrieval of Pubmed database as an example, the retrieval strategy is shown in Table 1.

2.2. Data collection and analysis
2.2.1. Research selections.
The 2 examiners (LXL and YQB) will independently conduct a literature search and select titles and abstracts according to the established inclusion and exclusion criteria. Then read the full text as needed for further evaluation. In the process of searching and evaluating the literature, any differences will be discussed and resolved with the third-party author (ZXD). For uncertain data, we will get in touch with the corresponding first author to determine whether this literature is included. Details of the process of the research are shown in the following chart (Fig. 1).

2.2.2. Extraction of data and information.
Detailed data and information extraction tables are as follows: basic information (first author, year of publication, country, year of study); year of study, characteristics of participants, sample size, race, age, results. When Shengyan Tan and others deal with the lost data, when the literature data is lost or unclear, it will be solved through discussion in the group and contacting the corresponding authors. the specific method can be obtained by contacting the corresponding author by e-mail. If the problem cannot be solved, a sensitivity analysis is conducted to determine the influence of the contained study in the whole outcome assessment.

2.2.3. Heterogeneity assessment.
We will use I^2 statistics to quantify statistical heterogeneity to assess the heterogeneity included in studies. The degree of heterogeneity is according to: $I^2 = 0\% \sim 40\%$, which may not be significant, $I^2 = 30\% \sim 60\%$, which can indicate moderate heterogeneity; $I^2 = 50\% \sim 90\%$, which can indicate considerable heterogeneity; $I^2 = 75\% \sim 100\%$, considerable heterogeneity.

2.2.4. Evaluation of studying quality.
The physiotherapy evidence database scale[9] will be utilized by 2 independent evaluators (LXL) to evaluate 11 quality areas of each included literature. The maximum score for each item is 10 (standard 1 does not score), including random allocation, hidden allocation, appropriate animal model, blind evaluation results, sample size calculation, and compliance with animal welfare regulations. Any differences will be resolved through discussion and negotiation with Xiping Chen.

2.2.5. Assessment of reporting deviations.
If there are more than 10 studies, funnel charts will be used to assess the potential for biases in small studies. If necessary, we will utilize Egger regression test and Begger correlation test to evaluate the publication bias.

2.2.6. Data synthesis.
All analyses will be carried out using Revman 5.3 software. The outcome indicators reported in the above study will be meta-analyzed. In this meta-analysis, we will use a stochastic model. If the I^2 test indicates unacceptable heterogeneity ($I^2 > 50\%$), we will conduct sensitivity analysis and subgroup analysis. If meta-analysis is not possible, the data will be carried out through a descriptive summary report. The probability value $P < .05$ is considered to be statistically significant.

2.2.7. Dubgroup analysis.
If there is any significant heterogeneity among the results, we will conduct a subgroup analysis: gene expression, study quality, sperm morphology.

2.2.8. Sensitivity analysis.
We will utilize sensitivity analysis to delete studies that do not conform to the HWE to assess the robustness and reliability of the summary results.

2.2.9. Quality of evidence.
We will use recommendation level, evaluation level, development level and evaluation level to assess the quality of these results. The results will be compartmentalized into 4 categories: very low, low, medium or high.[10]

3. Discuss

Insomnia is a wide range of sleep disorders caused by life events, or from a variety of pathophysiological causes, such as the effects of drugs, chronic diseases, and mental illness. Although there have been a large number of reports on the effects of sleep on the MRS. There are also many related animal studies, and the mechanism behind it is relatively well understood[11–12] High-quality evidence about the effects of sleep on the MRS is still lacking. However, the impact of sleep on the MRS is still unintelligible. We hope to find more practical and targeted results for determining the effects of sleep on the MRS in the recent systematic review and meta-analysis.

The advantages of this system review include: in order to avoid deviation, we will search the comprehensive literature as much as possible, including Chinese and English databases, and we will strictly evaluate the quality and extract the data. The deficiency of
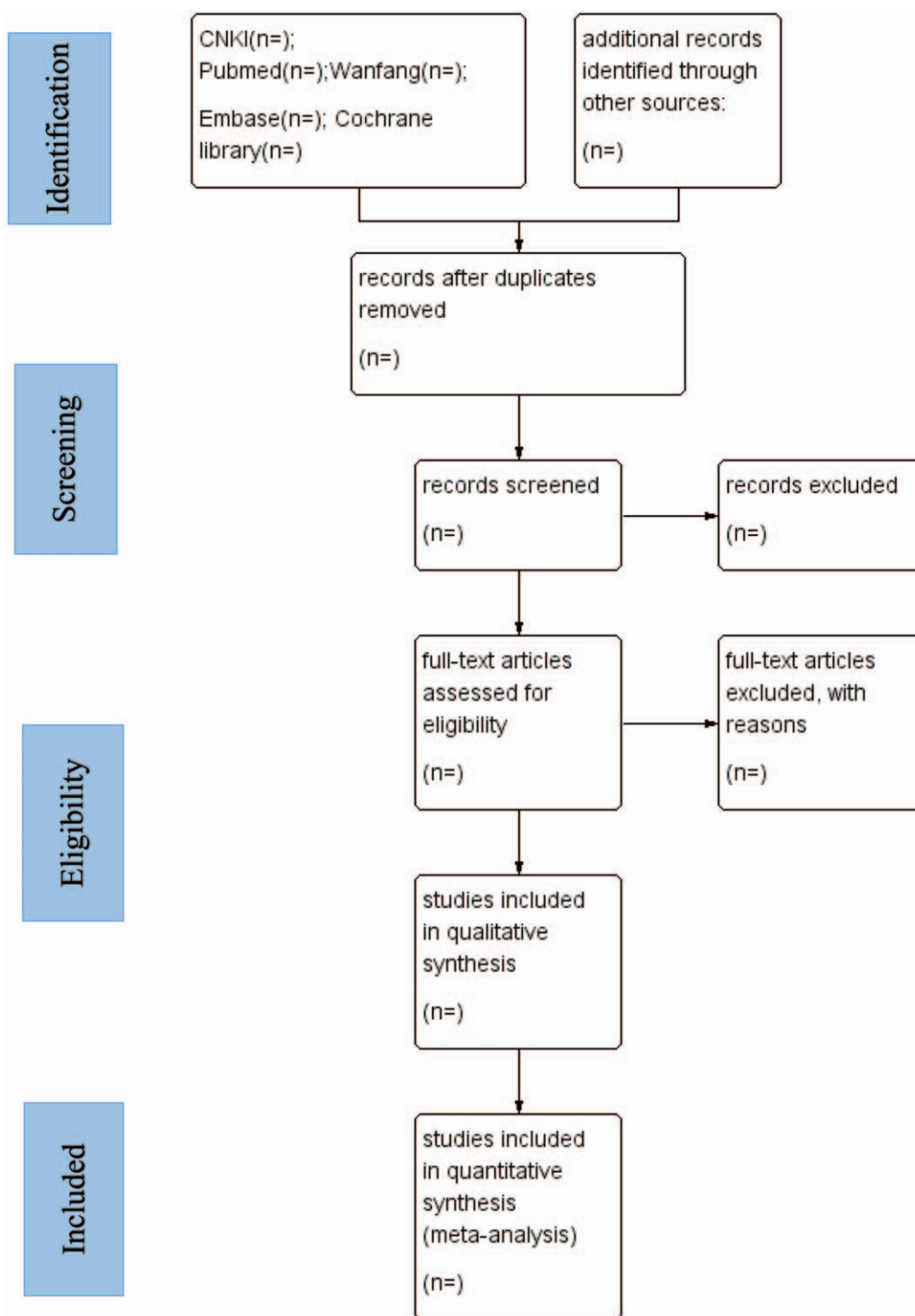
Figure 1. Flow chart of study selection.

this review is that we only search the most commonly used medical databases, which may deviate the results.

Author contributions

Shengyan Tan: project administration.
Xiang Gao: writing and drafting a plan.

Xiaodan Zhang and Wei huang: revising the protocol.
Xinglong Liu: research selection and data extraction.
Xiping Chen: resolving any differences.
Data curation: Xinglong Liu.
Project administration: Shengyan Tan.
Software: Wei Huang.
Supervision: Xiaodan Zhang.

Writing – original draft: Xiang Gao.
Writing – review & editing: Xiping Chen.

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